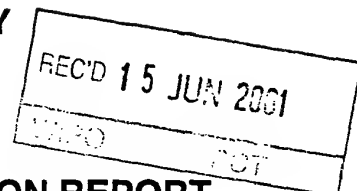


# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference PCT/MDC-Anker I	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/02299	International filing date (day/month/year) 09/03/2000	Priority date (day/month/year) 09/03/1999
International Patent Classification (IPC) or national classification and IPC A61K45/00		
Applicant MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 10 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  26/09/2000	Date of completion of this report  13.06.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Bochelen, D  Telephone No. +49 89 2399 8150  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02299

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-52 as originally filed

**Claims, No.:**

1-75 as originally filed

**Drawings, sheets:**

1/12-12/12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02299

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-27, 51, 72-75 with regard to industrial application.

because:

- ☒ the said international application, or the said claims Nos. 1-27, 51, 72-75 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

### IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/02299

- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☒ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-52, 72-75.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-52, 72-75
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-52, 72-75
Industrial applicability (IA)	Yes:	Claims	28-50, 52
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. A search report was established with regard to the general mechanism and the use of bile acids which are explicitly disclosed in the examples. Consequently, the applicant is informed that no International Preliminary Report will be established in respect of subject-matter which is not covered by the search report (Rule 66(1)(e) PCT).
2. **Claims 1-27, 51, 72-75** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item IV**

**Lack of unity of invention**

3. The International Examining Authority found multiple groups of invention in the present application.

The separate inventions are:

1. **Claims 1-52, 72-75:** use of inhibitors of endotoxin for the treatment of heart failure
2. **Claims 53-71:** use of inhibitors of endotoxin for the treatment of cachexia

The applicant neither restricted the claims nor paid additional fees for the examination of a supplementary invention, consequently this International Preliminary Report is established only for the first invention, i.e. **claims 1-52, 72-75**.

**Reasons**

**Reasons stated under Article 35(2) with regard to novelty, inventive step or**

**industrial applicability; citations and explanations supporting such statement**

4. Reference is made to the following documents:

- D1: SASATOMI K ET AL: 'Effects of ursodeoxycholic acid on intrahepatic localization of endotoxin in bile duct-ligated rats and patients with primary biliary cirrhosis.' GASTROENTEROLOGY, vol. 110, no. 4 SUPPL., 1996, page A1312 XP000971586 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week; San Francisco, California, USA; May 19-22, 1996 ISSN: 0016-5085
- D2: SASATOMI KURUMI ET AL: 'Abnormal accumulation of endotoxin in biliary epithelial cells in primary biliary cirrhosis and primary sclerosing cholangitis.' JOURNAL OF HEPATOLOGY, vol. 29, no. 3, 1998, pages 409-416, XP000971565 ISSN: 0168-8278
- D3: SASATOMI K ET AL: 'Effects of ursodeoxycholic acid on intrahepatic localization of endotoxin in patients with primary biliary cirrhosis.' JOURNAL OF ENDOTOXIN RESEARCH, vol. 3, no. SUPPL. 1, 1996, page 25 XP000971569 Fourth International Endotoxin Society Conference; Nagoya, Japan; October 22-25, 1996 ISSN: 0968-0519
- D4: POO JORGE L ET AL: 'Effects of ursodeoxycholic acid on hemodynamic and renal function abnormalities induced by obstructive jaundice in rats.' RENAL FAILURE, vol. 17, no. 1, 1995, pages 13-20, XP000971578 ISSN: 0886-022X
- D5: GREVE J W ET AL: 'BILE ACIDS INHIBIT ENDOTOXIN-INDUCED RELEASE OF TUMOR NECROSIS FACTOR BY MONOCYTES AN IN-VITRO STUDY' HEPATOLOGY, vol. 10, no. 4, 1989, pages 454-458, XP000971557 ISSN: 0270-9139
- D6: ANKER STEFAN D ET AL: 'Elevated soluble CD14 receptors and altered cytokines in chronic heart failure.' AMERICAN JOURNAL OF CARDIOLOGY, vol. 79, no. 10, 1997, pages 1426-1430, XP000971579 ISSN: 0002-9149
- D7: ANKER STEFAN D ET AL: 'Soluble CD14 receptors and cytokines in chronic heart failure: Immune activation due to endotoxin?' EUROPEAN HEART JOURNAL, vol. 18, no. ABSTR. SUPPL., 1997, page 297 XP000971584 XIXth Congress of the European Society of Cardiology together with the 32nd Annual General Meeting of the Association of

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP00/02299

European Paediatric Cardiologists;Stockholm, Sweden; August 24-28, 1997  
ISSN: 0195-668X

- D8: EGERER KARL R ET AL: 'Soluble CD14 receptors are increased in cachectic chronic heart failure suggesting a role for endotoxin.'  
CIRCULATION, vol. 94, no. 8 SUPPL., 1996, pages I672-I673,  
XP000971568 69th Scientific Sessions of the American Heart  
Association;New Orleans, Louisiana, USA; November 10-13, 1996 ISSN:  
0009-7322
- D9: NIEBAUER J ET AL: 'Endotoxin and immune activation in chronic heart failure patients with and without peripheral oedema.' EUROPEAN HEART JOURNAL, vol. 19, no. ABST. SUPPL., August 1998 (1998-08), page 174  
XP000971582 XXth Congress of the European Society of  
Cardiology;Vienna, Austria; August 22-26, 1998 ISSN: 0195-668X
- D10: NIEBAUER JOSEF ET AL: 'Endotoxin and immune activation in chronic heart failure: Proof of concept.' CIRCULATION, vol. 98, no. 17 SUPPL., 27 October 1998 (1998-10-27), page I27 XP000971576 71st Scientific Sessions of the American Heart Association;Dallas, Texas, USA; November 8-11, 1998 ISSN: 0009-7322
- D11: NIEBAUER J ET AL: 'Acute peripheral edema in patients with chronic heart failure is associated with endotoxemia and immune activation.' JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 31, no. 2 SUPPL. A, February 1998 (1998-02), page 155A XP000971591 47th Annual Scientific Session of the American College of Cardiology;Atlanta, Georgia, USA; March 29-April 1, 1998 ISSN: 0735-1097

**5. Novelty (Art. 33 (1) and (2) PCT):**

5.1 Documents D1-D4 deal with the effect of bile acids, like UCDA, on the intra-hepatic localization of endotoxin (D1-D3) and renal function (D4) in patients with cirrhosis or animal models of jaundice. None of these documents addresses the problem of chronic heart failure nor is a pharmaceutical composition comprising an endotoxin binding compound and diuretic disclosed therein. Consequently, these documents do not seem relevant for the novelty of the present application.

5.2 The prior art, as represented by the documents cited in the search report, does

not disclose the use of compounds that bind an endotoxin, e.g. a bile acid, for the treatment of chronic heart failure. Consequently, it is considered that the subject-matter of **claims 1-52 and 72-75** is new.

**6. Inventive step (Art. 33 (1) and (3) PCT):**

- 6.1 Documents D10 which is considered to be the closest prior art, discloses that in CHF patients with edema an endotoxin-induced immune activation occurs which results in increased levels of TNF $\alpha$  and TNF-R which can be normalized by diuretic treatment (D10: abstract). Documents D6-D9 and D11 as well describe the prevalence of endotoxin-induced immune activation in CHF patients. The subject-matter of **claims 1, 2, 28, 29, 34, 35, 37, 38, 40, 41, 51** differs in that compounds that affect endotoxin, e.g. bile acids, are used for the treatment of CHF by inhibiting immune activation. The problem to be solved may thus be regarded as to provide an alternative treatment for CHF. Document D5 discloses the inhibition of endotoxin-induced TNF production in monocytes by bile acids (see D5: p455-456). Moreover, bile acids are known to inhibit the translocation of endotoxin in the gut (D4: abstract; D2: p415 col2 §2). Therefore, it appears that the prior gives a clear hint to the skilled man for using bile acids for the treatment of CHF. Moreover, with regard to embodiments other than bile acids the application does not provide any evidence showing that endotoxin binding compounds would be useful for the treatment of CHF. The problem appears thus not to be solved. Consequently, it is considered that the subject-matter of **claims 1, 2, 28, 29, 34, 35, 37, 38, 40, 41, 51** does not involve an inventive step. The dependent **claims 3-27, 30-33, 39, 42-45, 72-75** do not contain any additional technical feature which would involve an inventive step.
- 6.2 With regard to the combination preparations that are subject-matter of **claims 46-50, 52** a skilled man would consider to combine endotoxin binding compounds with diuretics since it is known from document D10 that endotoxin levels can be normalized with diuretics. Hence, the subject-matter of **claims 46-50, 52** does not involve an inventive step.

**7. Industrial applicability (Art. 33 (1) and (4) PCT):**



For the assessment of the present **claims 1-27, 51, 72-75** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII**

**Certain observations on the international application**

8. **Claims 1, 2, 3-4, 8-10, 14, 17-18, 20-22, 28-29, 31-32, 37-38, 40-41, 47, 49-50** do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable the skilled person to determine which technical features are necessary to perform the stated functions:  
'compound that is able to reduce production, absorption and/or effect of an endotoxin' (**claims 1-2**), '..bind to an endotoxin' (**claims 3-4, 8, 28-29, 31-32, 47**), '..reduce the available endotoxin' (**claims 4, 10**), '..reduce absorption of endotoxin' (**claim 9**), '.. reduce ... the amount of free endotoxin' (**claims 14, 22**), '..inhibit the response..' (**claim 17, 37-38, 49**), '..to decrease the cytokine production (**claim 18**), '..to inhibit signalling..' (**claim 20**), '..reduce the permeability..' (**claim 21, 40-41, 50**), '..reduce he amount...that is able to translocate..' (**claim 22**).
9. It is clear from the description on pages 36-37 and figures 1-2 that the endotoxin, TNF $\alpha$  and CD14 are increased in oedematous CHF patients whereas CHF patients which are not oedematous have normal levels of endotoxin. Since independent **claims 1, 2, 28, 29, 34, 35, 37, 38, 40, 41** do not contain this feature it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.
10. The embodiments of the invention on pages 11 and 22 do not fall within the scope

of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

11. Although **claims 1, 28, 34, 37, 40 and 2, 29, 35, 38, 41** as well as **claims 46-50** have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection. Hence, **claims 1, 2, 28, 29, 34, 35, 37, 38, 40, 41, 46-50** do not meet the requirements of Article 6 PCT.
12. The omnibus **claims 51, 52, 72-75** are unclear and do not meet the requirements of Article 6 PCT.

**P NT COOPERATION TREATY**

**PCT**

**INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PCT/MDC-Anker</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 00/ 02299</b>	International filing date (day/month/year) <b>09/03/2000</b>	(Earliest) Priority Date (day/month/year) <b>09/03/1999</b>
Applicant  <b>MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.  
☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**USE OF INHIBITORS OF ENDOTOXIN FOR THE TREATMENT OF HEART FAILURE AND OF CACHEXIA**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 00/02299

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1-27, 43-45, 51, 53-75 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

**1. Claims: 1-52, 72-75**

Use of inhibitors of endotoxin for the treatment of heart failure

**2. Claims: 53-71**

Use of inhibitors of endotoxin for the treatment of cachexia

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

The expression "compound that is able to reduce the production, absorption and/or the effect of an endotoxin" encompasses an extremely large number of compounds that could have this mechanism of action, rendering a complete search impossible. The search had to be limited to the general mechanism and to the use of bile acids, which are explicitly used in the examples

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/02299

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K31/575 A61P9/04

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EP0-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	SASATOMI K ET AL: "Effects of ursodeoxycholic acid on intrahepatic localization of endotoxin in bile duct-ligated rats and patients with primary biliary cirrhosis." GASTROENTEROLOGY, vol. 110, no. 4 SUPPL., 1996, page A1312 XP000971586 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week; San Francisco, California, USA; May 19-22, 1996 ISSN: 0016-5085 the whole document  ----- -/--	1-75



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\* & \* document member of the same patent family

Date of the actual completion of the international search

15 March 2001

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Orviz Diaz, P

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/02299

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	SASATOMI KURUMI ET AL: "Abnormal accumulation of endotoxin in biliary epithelial cells in primary biliary cirrhosis and primary sclerosing cholangitis." JOURNAL OF HEPATOLOGY, vol. 29, no. 3, 1998, pages 409-416, XP000971565 ISSN: 0168-8278 page 415, right-hand column abstract ---	1-75
X,Y	SASATOMI K ET AL: "Effects of ursodeoxycholic acid on intrahepatic localization of endotoxin in patients with primary biliary cirrhosis." JOURNAL OF ENDOTOXIN RESEARCH, vol. 3, no. SUPPL. 1, 1996, page 25 XP000971569 Fourth International Endotoxin Society Conference; Nagoya, Japan; October 22-25, 1996 ISSN: 0968-0519 the whole document ---	1-75
X,Y	POO JORGE L ET AL: "Effects of ursodeoxycholic acid on hemodynamic and renal function abnormalities induced by obstructive jaundice in rats." RENAL FAILURE, vol. 17, no. 1, 1995, pages 13-20, XP000971578 ISSN: 0886-022X the whole document ---	1-75
X,Y	GREVE J W ET AL: "BILE ACIDS INHIBIT ENDOTOXIN-INDUCED RELEASE OF TUMOR NECROSIS FACTOR BY MONOCYTES AN IN-VITRO STUDY" HEPATOLOGY, vol. 10, no. 4, 1989, pages 454-458, XP000971557 ISSN: 0270-9139 the whole document ---	1-75
Y	ANKER STEFAN D ET AL: "Elevated soluble CD14 receptors and altered cytokines in chronic heart failure." AMERICAN JOURNAL OF CARDIOLOGY, vol. 79, no. 10, 1997, pages 1426-1430, XP000971579 ISSN: 0002-9149 the whole document ---	1-75
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/02299

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>ANKER STEFAN D ET AL: "Soluble CD14 receptors and cytokines in chronic heart failure: Immune activation due to endotoxin?"</p> <p>EUROPEAN HEART JOURNAL, vol. 18, no. ABSTR. SUPPL., 1997, page 297 XP000971584</p> <p>XIXth Congress of the European Society of Cardiology together with the 32nd Annual General Meeting of the Association of European Paediatric Cardiologists; Stockholm, Sweden; August 24-28, 1997 ISSN: 0195-668X the whole document</p>	1-75
Y	<p>EGERER KARL R ET AL: "Soluble CD14 receptors are increased in cachectic chronic heart failure suggesting a role for endotoxin."</p> <p>CIRCULATION, vol. 94, no. 8 SUPPL., 1996, pages I672-I673, XP000971568</p> <p>69th Scientific Sessions of the American Heart Association; New Orleans, Louisiana, USA; November 10-13, 1996 ISSN: 0009-7322 the whole document</p>	1-75
Y	<p>NIEBAUER J ET AL: "Endotoxin and immune activation in chronic heart failure patients with and without peripheral oedema."</p> <p>EUROPEAN HEART JOURNAL, vol. 19, no. ABST. SUPPL., August 1998 (1998-08), page 174 XP000971582</p> <p>XXth Congress of the European Society of Cardiology; Vienna, Austria; August 22-26, 1998 ISSN: 0195-668X the whole document</p>	1-52, 72-75
Y	<p>NIEBAUER JOSEF ET AL: "Endotoxin and immune activation in chronic heart failure: Proof of concept."</p> <p>CIRCULATION, vol. 98, no. 17 SUPPL., 27 October 1998 (1998-10-27), page I27 XP000971576</p> <p>71st Scientific Sessions of the American Heart Association; Dallas, Texas, USA; November 8-11, 1998 ISSN: 0009-7322 the whole document</p>	1-52, 72-75

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/02299

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>NIEBAUER J ET AL: "Acute peripheral edema in patients with chronic heart failure is associated with endotoxemia and immune activation." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 31, no. 2 SUPPL. A, February 1998 (1998-02), page 155A XP000971591 47th Annual Scientific Session of the American College of Cardiology;Atlanta, Georgia, USA; March 29-April 1, 1998 ISSN: 0735-1097 the whole document</p>	1-52, 72-75
Y	<p>SAKISAKA S ET AL: "BILIARY SECRETION OF ENDOTOXIN AND PATHOGENESIS OF PRIMARY BILIARY CIRRHOSIS" YALE JOURNAL OF BIOLOGY AND MEDICINE, NEW HAVEN, CT,US, vol. 70, no. 4, July 1997 (1997-07), pages 403-408, XP000971577 the whole document</p>	53-71

## PATENT COOPERATION TREATY

PCT

REC'D 29 DEC 2000

WIPO PCT/TO/2000

APR 2 2 2002

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>PCT-4027</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/IT99/00311</b>	International filing date (day/month/year) <b>06/10/1999</b>	Priority date (day/month/year) <b>09/10/1998</b>
International Patent Classification (IPC) or national classification and IPC <b>A61K31/22</b>		
Applicant <b>SIGMA-TAU HEALTHSCIENCE S.P.A. et al.</b>		

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MAR 29 2002

TECH CENTER 1600/2900

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 4 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand <b>18/04/2000</b>	Date of completion of this report <b>27.12.2000</b>
Name and mailing address of the international preliminary examining authority:  <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>	Authorized officer <b>Escolar Blasco, P</b> Telephone No. <b>+49 89 2399 7331</b> 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT99/00311

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

### Description, pages:

1-11 as originally filed

### Claims, No.:

1-9 with telefax of 04/08/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/IT99/00311

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*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	9
Inventive step (IS)	Yes:	Claims	1-8
	No:	Claims	9
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/IT99/00311

**Comments on item V**

1. Reference is made to the following documents:

D1: EP-A-0 773 020

D2: WO 98 33494 A

D3: WO 98 41113 A

2. Having regard to the present prior art the subject-matter of claims 1-8 seems to be novel, as none of the available prior art documents discloses the use of L-carnitine combined with trihydroxy or tetrahydroxystilbene for preparing a product for the prevention or treatment of neuronal or cerebral alterations brought about by ageing and use of neurotoxic drugs, cerebral stroke, loss of memory, presenile and senile dementia or Alzheimer's disease.
3. D1, D2 and D3 disclose the use of compositions containing L-carnitine (also acetyl or propionyl L-carnitine) and resveratrol for preventing or treating neuropathy or diabetic neuropathy (see the abstract of D1; the abstract, page 18, lines 28-30 and p.26, l.17-18 of D2; and claims 1, 2, 8, and p.4, l.11-22 of D3). Since neuropathy is a very general term, these documents would not allow the skilled in the art to deduce the further medical use claimed. Hence, claim 1 involves an inventive step.
- 3.1 Dependent claims 2-8 are allowable.
4. Claim 9 refers to a composition which differs from the prior art (D1, claim 1 and D3, claim 8) only in the presence of an indication specifying the therapeutical use of said composition. Such an indication is a mere presentation of information and therefore, not considered as a technical feature (Rule 67.1(v) PCT). As a consequence, claim 9 cannot be regarded as novel over the aforementioned documents D1 and D3.

## CLAIMS

1. Use of (A) L-carnitine or alkanoyl L-carnitine wherein the alkanoyl is a straight or branched-chain group containing 2-8 carbon atoms or a pharmacologically acceptable salt thereof, and (B) a trihydroxy or tetrahydroxystilbene to prepare a dietary supplement or a pharmaceutical product in which (A) and (B) are in admixture or separately packaged, for the prevention and treatment of pathological forms due to neuronal or cerebral alterations brought about by ageing and use of neurotoxic drugs, cerebral stroke, loss of memory, pre-senile and senile dementia and Alzheimer's disease.
2. Use according to claim 1, wherein the alkanoyl contains 2-6 carbon atoms.
3. Use according to claim 2, wherein the alkanoyl is selected from the group consisting of acetyl, propionyl, butyryl, valeryl and isovaleryl.
4. Use according to claims 1-3, wherein the component (B) is 3,4',5'-trihydroxystilbene (resveratrol) or 3,4',5'-trihydroxystilbene-3- $\beta$ -mono-D-glucoside or a pharmacologically acceptable salt or ester thereof.
5. Use according claim 4, wherein resveratrol is resveratrol extracted from *Vitis vinifera*, *Vitis rotundifolia* or *Vitis labrusca*.
6. Use according to claims 1-5, wherein the component (B) consists of extracts or natural products powders of grape's skin or of grape-stalks of *Vitis vinifera*, *Vitis rotundifolia* or *Vitis labrusca* and of *Polygonum cuspidatum* or *Polygonum multiflorum* roots.
7. Use according to claims 1-6, wherein the weight ratio (B):(A) is from 1:1 to 1:1.000.
8. Use according to claim 7, wherein the weight ratio (B):(A) is from 1:1 to 1:500.

04-08-2000

IT 009900311

13

9. Use according to claims 1-8 for the prevention or treatment of cerebral alterations due to ageing and use of neurotoxic drugs.

10. Use according to claim 9 for the prevention and treatment of cerebral stroke, loss of memory, and pre-senile and senile dementia and of Alzheimer's disease.

<sup>9</sup>  
11.

A container comprising:

(A) L-carnitine or an alkanoyl L-carnitine wherein the alkanoyl is a straight or branched-chain group containing 2-8 carbon atoms or a pharmacologically acceptable salt thereof, and

(B) a trihydroxy or tetrahydroxystilbene,

(A) and (B) being in admixture or separately packaged, the container bearing an indication that (A) and (B) are suitable to prevent/treat pathological forms due to neuronal or cerebral alterations.



09/98.0645

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
14 September 2000 (14.09.2000)

PCT

(10) International Publication Number  
WO 00/53224RECEIVED  
MAY 1 2000  
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- (51) International Patent Classification<sup>7</sup>: A61K 31/575, (DE). SCHUMANN, Ralf, Reiner [DE/DE]: Buchenallee  
A61P 9/04 104, D-16341 Zepernick (DE).
- (21) International Application Number: PCT/EP00/02299 (74) Agent: BAUMBACH, Fritz; Robert-Rössle-Strasse 10,  
D-13125 Berlin (DE).
- (22) International Filing Date: 9 March 2000 (09.03.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
- |           |                           |    |
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| 9905300.1 | 9 March 1999 (09.03.1999) | GB |
| 9905307.6 | 9 March 1999 (09.03.1999) | GB |
| 9905310.0 | 9 March 1999 (09.03.1999) | GB |
| 9905314.2 | 9 March 1999 (09.03.1999) | GB |
| 9905315.9 | 9 March 1999 (09.03.1999) | GB |
- (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): MAX-DELBÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN [DE/DE]; Robert-Rössle-Strasse 10, D-13125 Berlin (DE).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): ANKER, Stefan [DE/DE]; Hedrichplatz 25, D-10367 Berlin (DE). COATS, Andrew [AU/GB]; 105 A Cadogan Gardens, London SW3 2RF (GB). VOLK, Hans-Dieter [DE/DE]; Rathausstrasse 11, D-10178 Berlin (DE). RAUCHHAUS, Mathias [DE/DE]; Advokatenweg 40, D-06114 Halle
- Published:   
— with international search report
- (88) Date of publication of the international search report: 4 April 2002
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: USE OF INHIBITORS OF ENDOTOXIN FOR THE TREATMENT OF HEART FAILURE AND OF CACHEXIA

WO 00/53224 A3

(57) Abstract: A method of treating, preventing or ameliorating chronic heart failure or acute heart failure in a patient the method comprising administering to the patient an effective amount of: a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) molecule, for example LPS binding protein, BPI, lipoproteins, bile acids or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) molecule or bacterium in the gut, for example charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or chronic heart failure in a patient the method comprising administering to the patient an effective amount of: a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) molecule, for example LPS binding protein, BPI, lipoproteins, bile acids or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) molecule or bacterium in the gut, for example charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/02299

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/575 A61P9/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X, Y	<p>SASATOMI K ET AL: "Effects of ursodeoxycholic acid on intrahepatic localization of endotoxin in bile duct-ligated rats and patients with primary biliary cirrhosis."</p> <p>GASTROENTEROLOGY, vol. 110, no. 4 SUPPL., 1996, page A1312 XP000971586</p> <p>96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week; San Francisco, California, USA; May 19-22, 1996</p> <p>ISSN: 0016-5085</p> <p>the whole document</p> <p style="text-align: center;">--- -/--</p>	1-75



Further documents are listed in the continuation of box C



Patent family members are listed in annex

\* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

15 March 2001

Date of mailing of the international search report

15 March 2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax (+31-70) 340-3016

Authorized officer

Orviz Diaz, P

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/02299

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X,Y	SASATOMI KURUMI ET AL: "Abnormal accumulation of endotoxin in biliary epithelial cells in primary biliary cirrhosis and primary sclerosing cholangitis." JOURNAL OF HEPATOLOGY, vol. 29, no. 3, 1998, pages 409-416. XP000971565 ISSN: 0168-8278 page 415, right-hand column abstract ---	1-75
X,Y	SASATOMI K ET AL: "Effects of ursodeoxycholic acid on intrahepatic localization of endotoxin in patients with primary biliary cirrhosis." JOURNAL OF ENDOTOXIN RESEARCH, vol. 3, no. SUPPL. 1, 1996, page 25 XP000971569 Fourth International Endotoxin Society Conference; Nagoya, Japan; October 22-25, 1996 ISSN: 0968-0519 the whole document ---	1-75
X,Y	POO JORGE L ET AL: "Effects of ursodeoxycholic acid on hemodynamic and renal function abnormalities induced by obstructive jaundice in rats." RENAL FAILURE, vol. 17, no. 1, 1995, pages 13-20. XP000971578 ISSN: 0886-022X the whole document ---	1-75
X,Y	GREVE J W ET AL: "BILE ACIDS INHIBIT ENDOTOXIN-INDUCED RELEASE OF TUMOR NECROSIS FACTOR BY MONOCYTES AN IN-VITRO STUDY" HEPATOLOGY, vol. 10, no. 4, 1989, pages 454-458. XP000971557 ISSN: 0270-9139 the whole document ---	1-75
Y	ANKER STEFAN D ET AL: "Elevated soluble CD14 receptors and altered cytokines in chronic heart failure." AMERICAN JOURNAL OF CARDIOLOGY, vol. 79, no. 10, 1997, pages 1426-1430. XP000971579 ISSN: 0002-9149 the whole document ---	1-75
	--- -/--	

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	<p>ANKER STEFAN D ET AL: "Soluble CD14 receptors and cytokines in chronic heart failure: Immune activation due to endotoxin?"</p> <p>EUROPEAN HEART JOURNAL, vol. 18, no. ABSTR. SUPPL., 1997, page 297 XP000971584</p> <p>XIXth Congress of the European Society of Cardiology together with the 32nd Annual General Meeting of the Association of European Paediatric Cardiologists; Stockholm, Sweden; August 24-28, 1997 ISSN: 0195-668X the whole document</p>	1-75
Y	<p>EGERER KARL R ET AL: "Soluble CD14 receptors are increased in cachectic chronic heart failure suggesting a role for endotoxin."</p> <p>CIRCULATION, vol. 94, no. 8 SUPPL., 1996, pages I672-I673, XP000971568</p> <p>69th Scientific Sessions of the American Heart Association; New Orleans, Louisiana, USA; November 10-13, 1996 ISSN: 0009-7322 the whole document</p>	1-75
Y	<p>NIEBAUER J ET AL: "Endotoxin and immune activation in chronic heart failure patients with and without peripheral oedema."</p> <p>EUROPEAN HEART JOURNAL, vol. 19, no. ABST. SUPPL., August 1998 (1998-08), page 174 XP000971582</p> <p>XXth Congress of the European Society of Cardiology; Vienna, Austria; August 22-26, 1998 ISSN: 0195-668X the whole document</p>	1-52, 72-75
Y	<p>NIEBAUER JOSEF ET AL: "Endotoxin and immune activation in chronic heart failure: Proof of concept."</p> <p>CIRCULATION, vol. 98, no. 17 SUPPL., 27 October 1998 (1998-10-27), page I27 XP000971576</p> <p>71st Scientific Sessions of the American Heart Association; Dallas, Texas, USA; November 8-11, 1998 ISSN: 0009-7322 the whole document</p>	1-52, 72-75

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/02299

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	<p>NIEBAUER J ET AL: "Acute peripheral edema in patients with chronic heart failure is associated with endotoxemia and immune activation."</p> <p>JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 31, no. 2 SUPPL. A, February 1998 (1998-02), page 155A XP000971591 47th Annual Scientific Session of the American College of Cardiology;Atlanta, Georgia, USA; March 29-April 1, 1998 ISSN: 0735-1097 the whole document</p>	<p>1-52, 72-75</p>
Y	<p>SAKISAKA S ET AL: "BILIARY SECRETION OF ENDOTOXIN AND PATHOGENESIS OF PRIMARY BILIARY CIRRHOSIS"</p> <p>YALE JOURNAL OF BIOLOGY AND MEDICINE, NEW HAVEN, CT,US, vol. 70, no. 4, July 1997 (1997-07), pages 403-408, XP000971577 the whole document</p>	<p>53-71</p>

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 00/02299

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1-27, 43-45, 51, 53-75 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The expression "compound that is able to reduce the production, absorption and/or the effect of an endotoxin" encompasses an extremely large number of compounds that could have this mechanism of action, rendering a complete search impossible. The search had to be limited to the general mechanism and to the use of bile acids, which are explicitly used in the examples

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-52, 72-75

Use of inhibitors of endotoxin for the treatment of heart failure

2. Claims: 53-71

Use of inhibitors of endotoxin for the treatment of cachexia



# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C. 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 13 October 2000 (13.10.00)	<b>Applicant's or agent's file reference</b> PCT/MDA-Anker
<b>International application No.</b> PCT/EP00/02299	<b>Priority date (day/month/year)</b> 09 March 1999 (09.03.99)
<b>International filing date (day/month/year)</b> 09 March 2000 (09.03.00)	<b>Priority date (day/month/year)</b> 09 March 1999 (09.03.99)
<b>Applicant</b> ANKER, Stefan et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
26 September 2000 (26.09.00)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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